IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF NORTH CAROLINA

NATERA, INC., Plaintiff,	)	
v.	)	1:23-CV-629
NEOGENOMICS LABORATORIES, INC., Defendant.	)	

CLAIM CONSTRUCTION ORDER

In July 2023, Natera Inc. sued NeoGenomics Laboratories, Inc., asserting that NeoGenomics' medical diagnostic product infringes two of Natera's method patents. This matter is before the Court for claim construction of certain terms in those patents. The parties dispute the meaning of terms and sets of terms found in Claim 1 of U.S. Patent No. 11,519,035 (the "'035 patent") and Claims 1 and 14 of U.S. Patent No. 11,530,454 (the "'454 patent"). The disputed claim terms are construed herein and summarized in the attached Appendix.

NeoGenomics also contends that the '454 patent contains terms incapable of construction that render the patent invalid for indefiniteness. Because NeoGenomics has not presented clear and convincing evidence that the disputed claims fail to inform a person skilled in the art about the scope of the invention with reasonable certainty, the patent is not invalid.

I. Introduction

Natera is the owner of the '035 and '454 patents. *See* Doc. 1-2; Doc. 1-1. The company uses the methods described in these two patents in its Signatera product, a test that is used for early detection of cancer recurrence. Doc. 9-18 at 2–3.[1] NeoGenomics has a competing product called RaDaR. Doc. 94 at ¶ 10; *see also* Doc. 169 at 2-4 (order giving overview of the two products). Natera contends that NeoGenomics' RaDaR product infringes the methods claimed in the '035 and '454 patents.

In mid-March, the parties submitted a joint claim construction statement. Doc. 249. They have since briefed their proposed claim constructions and NeoGenomics' indefiniteness challenge. *See* Doc. 262; Doc. 264; Doc. 271; Doc. 272. At a Markman hearing held on May 14, 2024, the parties presented argument and evidence in support of their proposed constructions. Minute Entry 05/14/2024. NeoGenomics also presented its indefiniteness arguments and Natera was given the opportunity to respond.

II. Claim Construction

The scope of a patent is defined by its claims. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). "The words of a claim are generally given their ordinary and customary meaning" which is "the meaning that the terms would have to a person of ordinary skill in the art at the time of invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (cleaned up).

[1] All page citations are to the pagination appended by the CM-ECF system.

A person of ordinary skill in the art views a term in the greater context of the patent itself, including the other claims and the specification. *Id.* at 1313. If it is in evidence, courts construing claims can also consider the prosecution history. *Id.* at 1317; *Vitronics*, 90 F.3d at 1582. Often the intrinsic evidence alone can reveal the meaning of a claim term. *Vitronics*, 90 F.3d at 1583. If necessary, courts can also look to extrinsic evidence like expert testimony. *See Phillips*, 415 F.3d at 1317; *see also Aristocrat Techs. Austl. Pty Ltd. v. Int'l Game Tech.*, 709 F.3d 1348, 1355, 1358 (Fed. Cir. 2013) (stating courts can consider extrinsic evidence, but there is "no reason to resort to consideration of extrinsic evidence" when claim term is clear and support is found in specification).

III. Disputed Claim Terms in the '035 Patent

The parties dispute the meaning of two sets of terms in Claim 1 of the '035 patent. With the disputed terms highlighted in yellow, Claim 1 states:

> A method for amplifying and sequencing DNA, comprising:
> tagging isolated cell free DNA with one or more universal tail adaptors to generate tagged products, wherein the isolated cell-free DNA is isolated from a blood sample collected from a subject who is not a pregnant women;
> amplifying the tagged products one or more times to generate final amplification products, wherein one of the amplification steps comprises targeted amplification of a plurality of single nucleotide polymorphism (SNP) loci in a single reaction volume, wherein one of the amplifying steps introduces a barcode and one or more sequencing tags; and
> sequencing the plurality of SNP loci on the cell free DNA by conducting massively parallel sequencing on the final amplification products, wherein the plurality of SNP loci comprises 25–2,000 loci associated with cancer.

Doc. 1-2 at 213.

A. "amplifying the tagged products . . .wherein one of the amplification steps comprises targeted amplification"

The parties first dispute the meaning of the terms "amplifying the tagged products . . . wherein one of the amplification steps comprises targeted amplification." Their proposed constructions are below:

Claim	Natera's Construction	NeoGenomics' Construction
"amplifying the tagged products … wherein one of the amplification steps comprises targeted amplification."	Plain and ordinary meaning.	This step is separate from and must occur after completion of (and therefore must use distinct PCR primers from) the step of "tagging . . . with one or more universal tail adapters to generate tagged products."

The parties agree that "amplifying the tagged products" is a separate step from "tagging isolated cell-free DNA with one or more universal tail adapters to generate tagged products." Doc. 262 at 7; *see also* Doc. 264 at 11. NeoGenomics explains that its construction requires that the amplifying and tagging steps of Claim 1 use distinct primers and occur in two separate PCR processes. Doc. 264 at 11–14. Natera contends that NeoGenomics' construction imposes a limitation on the claim that was not include in the claim's language and that tagging and amplifying can occur in the same PCR process. Doc. 262 at 7–11.

The Court adopts Natera's construction. NeoGenomics' construction would "read unstated limitations into claim language." *N. Telecom Ltd. v. Samsung Elecs., Co.*, 215 F.3d 1281, 1290 (Fed. Cir. 2000); *see also* Doc. 169 at 6.

B. "SNP loci … associated with cancer"

The parties dispute the meaning of the set of terms "SNP loci … associated with cancer" found in Claim 1 of the '035 patent. Their proposed constructions are below:

Claim	Natera's Construction	NeoGenomics' Construction
"SNP loci … associated with cancer"	Plain and ordinary meaning.	"A single nucleotide that may differ between the genomes of two members of the same species and is associated with cancer."

NeoGenomics contends that its proposed construction applies the definition explicitly included in the patent. Doc. 264 at 8. Natera contends that the terms should be construed to include variants "between cancer cells and the other cells within a person's body, not just variants that differ between two members of a species," Doc. 262 at 11–12, but it does not include that language in its proposed construction.

A claim should be read "in view of the specification," which is highly relevant to claim construction. *Phillips*, 415 F.3d at 1315. A patentee can choose to define claim terms, and when a patent specification "expressly defines terms used in the claims" the specification is treated as a dictionary. *Vitronics*, 90 F.3d at 1582; *see also BookIT Oy v. Bank of Am. Corp.*, 817 F. App'x 990, 994 (Fed. Cir. 2020) (stating "[t]here can be no clearer definitions than those expressly recited in the patent" and affirming district court's decision to use definitions included in specification). The definition given in the specification governs, even if it differs from the ordinary and customary meaning. *Phillips*, 415 F.3d at 1316.

Under a "Definitions" section in the '035 patent specification, the term "single nucleotide polymorphism" ("SNP") is defined as "a single nucleotide that may differ between the genomes of two members of the same species. The usage of the term should not imply any limit on the frequency with which each variant occurs." Doc. 1-2 at 105 (col. 34:46–50). "The term" referenced in the first sentence is "SNP."

The term "locus" is also defined in this section. *Id.* (col. 34:58–62). "Locus refers to a particular region of interest on the DNA (or corresponding RNA) of an individual, which may refer to a SNP . . ." *Id.* (col. 34: 58–60). Both parties agree that the term "loci" means single nucleotide positions. *See* Doc. 262 at 11; Doc. 264 at 9–10.

While the Court agrees with NeoGenomics that the definition of SNP expressly given in the patent governs, *see Vitronics*, 90 F.3d at 1582, NeoGenomics has not included the entire definition in its proposed construction. The Court will include the second sentence of the definition for clarity and accuracy. Using that definition and explicitly stating that "the term" referenced in the second sentence is "SNP," the Court construes "SNP loci … associated with cancer" to mean "a single nucleotide that may differ between the genomes of two members of the same species and is associated with cancer. The usage of the term 'SNP' should not imply any limit on the frequency with which each variant occurs."

As part of its responsive claim construction brief, Natera submitted an expert declaration to support its construction of "SNP loci … associated with cancer." Doc. 273. NeoGenomics' motion to strike this expert testimony, Doc. 276, is discussed below. *See* VI. Motion to Strike *infra* p. 14.

IV. Disputed Claim Terms in the '454 Patent

With disputed terms highlighted in yellow, Claim 1 of the '454 patent states:

> A method for preparing a plasma sample of a subject having cancer or suspected of having cancer … the method comprising:
>
> performing whole exome sequencing or whole genome sequencing on a tumor sample of the subject to identify a plurality of tumor-specific SNV mutations;
>
> performing targeted multiplex amplification to amplify 10 to 500 target loci each encompassing a different tumor-specific SNV mutation from cell-free DNA isolated from a plasma sample of the subject or DNA derived therefrom to obtain amplicons having a length of 50–150 bases, wherein the target loci are amplified together in the same reaction volume; and
>
> sequencing the amplicons to obtain sequence reads, and detecting one or more of the tumor-specific SNV mutations present in the cell-free DNA from the sequence reads, wherein the sequencing has a depth of read of at least 50,000 per target locus.

Doc. 1-1 at 222. Claim 14 contains much of the same language as Claim 1, and the contested terms and sets of terms are included in both claims. For purposes of claim construction, Claim 1 is representative. *See* Doc. 262 at 15, n.8; *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1334 (Fed. Cir. 2003) (holding "the same claim term in the same patent … carries the same construed meaning" unless reason exists to find otherwise).

A. "sequencing the amplicons"

The parties' proposed constructions are below:

Claim	Natera's Construction	NeoGenomics' Construction
"sequencing the amplicons"	Plain and ordinary meaning.	"Sequencing the amplicons obtained from the targeted multiplex amplification step."

NeoGenomics contends that "the amplicons" referred to in the phrase "sequencing the amplicons" must be the amplicons obtained from the immediately preceding targeted multiplex amplification step in Claim 1 and that no intervening steps can occur between multiplex amplification and sequencing. Doc. 264 at 15. According to Natera, a person of ordinary skill in the art would understand this set of terms to allow "intermediate steps after multiplex amplification but before sequencing." Doc. 262 at 16.

NeoGenomics is correct that the sequencing must be done on the amplicons obtained from the targeted multiplex amplification, not on some other set of amplicons obtained from some other source or process; the term "the" must mean something. But Claim 1 does not say that the method prohibits the performance of additional steps on the amplicons before they are sequenced, and it does not require sequencing of the amplicons obtained directly and without modification from the multiplex amplification step, as NeoGenomics contends.

First, Claim 1 is an open-ended, independent claim that "does not exclude additional, unrecited elements or method steps." *CollegeNet, Inc. v. ApplyYourself, Inc.*, 418 F.3d 1225, 1235 (Fed. Cir. 2005) (cleaned up). The claim should not be read to prohibit application of additional, unrecited steps to the amplicons before the amplicons are sequenced, so long as what is being sequenced are those amplicons.

Second, the rest of the '454 patent specification supports applying the plain and ordinary meaning. Claim 11 depends on Claim 1 and "comprises performing barcoding PCR prior to the sequencing." Doc. 1-1 at 222. "[I]f a dependent claim reads on a

particular embodiment of the claimed invention, the corresponding independent claim must cover that embodiment as well." *Littlefuse, Inc. v. Mersen USA EP Corp.*, 29 F.4th 1376, 1380 (Fed. Cir. 2022). Thus Claim 1 must allow steps before sequencing.

NeoGenomics contends that Claim 11 still has meaning under its construction because barcoding PCR could be performed before the multiplex amplification step and thus would be performed before sequencing. Doc. 264 at 17. It further states that the specification includes examples where barcoding PCR occurs at this point. *See id.*; *see also* Doc. 1-1 at 186 (col. 99:12–22, 99:47–49). But the specification also includes examples and embodiments where steps are performed after multiplex amplification and before sequencing. Doc. 1-1 at 218 (col. 163:52–59, 164:19–28). NeoGenomics' construction would unnecessarily read embodiments out of the written description and unstated limitations into the claims.[2] *See Samsung*, 215 F.3d at 1290; *CollegeNet*, 418 F.3d at 1231 (stating courts should not "import limitations from the specification into the claims"); *Source Vagabond Sys. Ltd. v. Hydrapak, Inc.*, 753 F.3d 1291, 1299–1300 (Fed. Cir. 2014) (rejecting construction that read in extra terms and contradicted specification).

NeoGenomics cites to the patent prosecution of a different patent in support of its construction. Doc. 264 at 17–20. The claim in that patent contains different language, and the Court is not convinced this prosecution history is relevant.

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[2] NeoGenomics cited *Guardant Health Inc. v. Found. Med., Inc.*, in its briefing and during oral argument for the proposition that the word "the" requires Claim 1 to mean sequencing the amplicons obtained directly from the multiplex amplification without any intervening steps. *See* Doc. 264 at 15–17; *see also Guardant*, No. 17-CV-1616, 2019 WL 5677748 (D. Del. Nov. 1, 2019), *adopted by* No. 17-CV-1616, 2020 WL 1329513 (D. Del. Mar. 23, 2020). That case turns on its own facts and does not require a different result here.

The Court adopts Natera's construction.

B. "sequencing the amplicons to obtain sequence reads, and detecting one or more of the tumor-specific SNV mutations present in the cell-free DNA from the sequence reads"

The parties' different proposed constructions are included below:

Claim	Natera's Construction	NeoGenomics' Construction
"sequencing the amplicons to obtain sequence reads, and detecting one or more of the tumor-specific SNV mutations present in the cell-free DNA from the sequence reads"	The terms are part of one sequencing step.	Plain and ordinary meaning, which is that "detecting … from the sequence reads" is performed on the sequence reads generated by the claimed sequencing step, and not part of the claimed sequencing step.

Natera points to the entire structure of Claim 1 to say that the terms, read in the larger context of the claim, indicate that the sequencing and detecting steps happen in the same sequencing process. Doc. 262 at 21–22. NeoGenomics contends that the detecting step is performed on the sequence reads obtained from sequencing; in other words, the sequencing and detecting steps are separate. Doc. 264 at 20–22. NeoGenomics also points to the syntax of the claim and the specification in support. *Id.* at 21–22.

"A claim must be read in accordance with the precepts of English grammar." *In re Hyatt*, 708 F.2d 712, 714 (Fed. Cir. 1983); *see also Mformation Techs., Inc. v. Rsch. in Motion Ltd.*, 764 F.3d 1392, 1398 (Fed. Cir. 2014) (holding a claim may, "as a matter of logic or grammar," require an order); *Tris Pharma, Inc. v. Teva Pharmas. USA, Inc.*, No. 20-CV-5212, 2021 WL 3879153, at *3 (D.N.J. Aug. 25, 2021) (stating a person of ordinary skill in the art "still follows the basics of English"). A claim does not require an

order of steps unless it recites an order, the specification requires an order, or an order is clearly required by the rules of grammar or logic. *Mformation*, 764 F.3d at 1398–99.

The structure of Claim 1 of the '454 patent indicates that the sequencing and detecting are all part of one sequencing step. Three discrete steps of Claim 1, the steps that begin "performing," "performing," and "sequencing," have hanging indents and are separated by semi-colons. Doc. 1-2 at 222. In contrast, the detecting language is included in the sequencing step and is only offset by a comma. The sequencing is done to detect SNVs, and the structure of the claim indicates that the detecting and sequencing are part of the same step.

The Court adopts Natera's construction.

V. Indefiniteness

A patent's claims must "particularly point out and distinctly claim the subject matter which the applicant regards as his invention." 35 U.S.C. § 112 (cleaned up). A patent is invalid for indefiniteness if "its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014). The burden of proof requires clear and convincing evidence from the party asserting indefiniteness. *BASF Corp. v. Johnson Matthey Inc.*, 875 F.3d 1360, 1365 (Fed. Cir. 2017).

A. "clonal" and "subclonal"

NeoGenomics contends that the terms "clonal" and "subclonal" found in the '454 patent cannot be construed because they are indefinite. Doc. 264 at 22–25. Both parties'

experts have the same understanding of the two terms: mutations that are present in all of a tumor's cells are clonal, while mutations that are found in some but not all of a tumor's cells are subclonal. *See* Doc. 263 at ¶¶ 23–24 (Natera's expert declaration); Doc. 264-5 at ¶¶ 21–22 (NeoGenomics' expert declaration). Subclonal mutations may form as cancer cells continue to divide and propagate. *See* Doc. 263 at ¶ 24; Doc. 264-5 at ¶ 22.

NeoGenomics contends that the patent "provides no guidance as to how to choose the frame of reference to differentiate between a clonal and subclonal mutation," Doc. 264 at 24, guidance that is necessary to give notice of what methods would or would not infringe the claims. But the agreed-upon meanings of the terms themselves provide the way they are differentiated: a mutation detected in all sampled areas of a tumor is clonal while a mutation detected in some but not all sampled areas is subclonal. *Icon Health & Fitness*, cited by NeoGenomics is distinguishable; there the terms themselves were ambiguous and that is not the case here. *See Icon Health & Fitness, Inc. v. Polar Electro Oy*, 656 F. App'x 1008, 1014–15 (2016). NeoGenomics has not shown by clear and convincing evidence that these terms render their corresponding claims indefinite.

B. "present in less than or equal to 0.015% of the cell-free DNA comprising the SNV locus" and "present in 0.005% to 0.015% of the cell-free DNA comprising the SNV locus"

NeoGenomics contends that Claims 14 and 28 of the '454 patent require a limit of detection. Doc. 264 at 27. According to NeoGenomics, more than one method of calculating a limit of detection exists, these methods can lead to different results, and the patent does not give guidance on the correct method or correct way to choose a method.

Id. at 26–28. This means, NeoGenomics says, that a person of ordinary skill in the art would not know which method to choose or whether a chosen method is covered by the claims; thus Claims 14 and 28 are indefinite. *Id.* Natera says that this reading overcomplicates the issue by requiring more than the claims demand. Doc. 262 at 25–26.

NeoGenomics offers insufficient evidence in support of its contentions. The claim does not recite a limit of detection, and there is nothing persuasive to indicate that the way the method's limit of detection is calculated matters, unlike in *Dow Chemical* where the term at issue was expressly included in the claim and was not a term of art. *See Dow Chem. Co. v. Nova Chems. Corp. (Can.)*, 803 F.3d 620, 631, 635 (Fed. Cir. 2015) (stating term at issue was "a new Dow construct" and finding claim indefinite because calculation of value required directly in claim could be done various ways that yielded different results). Any method capable of detecting an SNV mutation present below or within the prescribed ranges of the claims will do. And examples found in the specification should not be read to limit the claim language. *See Conoco, Inc. v. Energy & Env't Int'l, L.C.*, 460 F.3d 1349, 1358 (Fed. Cir. 2006).

NeoGenomics does not offer clear and convincing evidence that a person of ordinary skill in the art would not know how to choose a method capable of detecting SNV mutations within the claimed thresholds or that claims containing this requirement are indefinite.

VI. Motion to Strike

Natera submitted an expert declaration as evidence with its responsive claim construction brief. *See* Doc. 273. The expert's testimony was directed to whether

acquired and inherited mutations are covered by the term "SNP loci … associated with cancer" found in Claim 1 of the '035 patent. *See* Doc. 272 at 10–14. NeoGenomics moves to strike portions of this declaration. Doc. 276. It contends that Natera offers a new construction in its response brief and NeoGenomics is prejudiced by the expert testimony because it did not have the opportunity to respond. Doc. 275 at 4.

The issue of whether "SNP loci … associated with cancer" covers both acquired and inherited mutations is not before the Court as an issue of claim construction. Neither party asked for constructions that use the terms "acquired" or "inherited" or otherwise asked to include any construction resolving this issue, and the question only began to crystallize with the response briefs. To the extent this matters, it can be addressed in dispositive motions on infringement.

While the Court did not consider the declaration in resolving claim construction issues, the Court will deny the motion to strike so the record is complete and so that the testimony does not have to be resubmitted at summary judgment.

It is **ORDERED** that:

1. The defendant's motion to strike, Doc. 276, is **DENIED**.
2. The claims at issue are **CONSTRUED** as set forth herein and summarized in the attached chart.

This the 17th day of May, 2024.

UNITED STATES DISTRICT JUDGE

Appendix

Patent & Claim	Claim Language	Natera's Proposed Construction	NeoGenomics' Proposed Construction	Court's Construction
'035 patent, Claim 1	"amplifying the tagged products … wherein one of the amplification steps comprises targeted amplification"	Plain and ordinary meaning.	This step is separate from and must occur after completion of (and therefore must use distinct PCR primers from) the step of "tagging . . . with one or more universal tail adapters to generate tagged products."	Plain and ordinary meaning.
'035 patent, Claim 1	"SNP loci … associated with cancer"	Plain and ordinary meaning.	"A single nucleotide that may differ between the genomes of two members of the same species and is associated with cancer"	"A single nucleotide that may differ between the genomes of two members of the same species and is associated with cancer. The usage of the term 'SNP' should not imply any limit on the frequency with which each variant occurs."
'454 patent, Claims 1 and 14	"sequencing the amplicons"	Plain and ordinary meaning.	"Sequencing the amplicons obtained from the targeted multiplex amplification step"	Plain and ordinary meaning.

'454 patent, Claims 1 and 14	"sequencing the amplicons to obtain sequence reads, and detecting one or more of the tumor-specific SNV mutations present in the cell-free DNA from the sequence reads"	The terms are part of one sequencing step.	Plain and ordinary meaning, which is that "detecting...from the sequence reads" is performed on the sequence reads generated by the claimed sequencing step, and not part of the claimed sequencing step.	The terms are part of one sequencing step.
'454 patent, Claims 3, 5, 17, 19	"clonal"	Not indefinite; plain and ordinary meaning.	Claim is indefinite and not amenable to construction.	Plain and ordinary meaning.
'454 patent, Claims 4, 5, 18, 19	"subclonal"	Not indefinite; plain and ordinary meaning.	Claim is indefinite and not amenable to construction.	Plain and ordinary meaning.
'454 patent, Claim 14	"present in less than or equal to 0.015% of the cell-free DNA comprising the SNV locus"	Not indefinite; plain and ordinary meaning.	Claim is indefinite and not amenable to construction.	Plain and ordinary meaning.
'454 patent, Claim 28	"present in 0.005% to 0.015% of the cell-free DNA comprising the SNV locus"	Not indefinite; plain and ordinary meaning.	Claim is indefinite and not amenable to construction.	Plain and ordinary meaning.